ISOLATED RENAL CELLS AND USES THEREOF

RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. §119(e) to U.S. provisional application Nos. 61/114,025, filed Nov. 12, 2008, 61/114,030, filed Nov. 12, 2008, 61/201,056, filed Dec. 5, 2008, 61/201,305, filed Dec. 8, 2008, and 61/121,311, filed Dec. 10, 2008, the entire contents of which are incorporated herein by reference. The subject matter of the present application is related to U.S. Provisional Application No. 61/260,833 filed on Nov. 12, 2009, the disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention is directed to isolated renal cells, including tubular and erythropoietin (EPO)-producing kidney cell populations, and methods of isolating and culturing the same, as well as methods of treating a subject in need with the cell populations.

BACKGROUND OF THE INVENTION

[0003] Chronic Kidney Disease (CKD) affects over 19M people in the United States and is frequently a consequence of metabolic disorders involving obesity, diabetes, and hypertension. Examination of the data reveals that the rate of increase is due to the development of renal failure secondary to hypertension and non-insulin dependent diabetes mellitus (NIDDM) (United States Renal Data System: Costs of CKD and ESRD. ed. Bethesda, Md., National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007 pp 223-238)—two diseases that are also on the rise worldwide. Obesity, hypertension, and poor glycemic control have all been shown to be independent risk factors for kidney damage, causing glomerular and tubular lesions and leading to proteinuria and other systemically-detectable alterations in renal filtration function (Aboushwareb, et al., World J Urol, 26: 295-300, 2008; Amann, K. et al., Nephrol Dial Transplant, 13: 1958-66, 1998). CKD patients in stages 1-3 of progression are managed by lifestyle changes and pharmacological interventions aimed at controlling the underlying disease state(s), while patients in stages 4-5 are managed by dialysis and a drug regimen that typically includes anti-hypertensive agents, erythropoiesis stimulating agents (ESAs), iron and vitamin D supplementation. According to the United States Renal Data Service (USRDS), the average end-stage renal disease (ESRD) patient expends >$600 per month on injectable erythropoiesis-stimulating agents (ESAs), Vitamin D supplements, and iron supplements (United States Renal Data System: Costs of CKD and ESRD. ed. Bethesda, Md., National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007 pp 223-238). When paired with the annual average cost of dialysis ($65,405), the healthcare cost for maintenance of a single patient rises to >$72,000/yr (United States Renal Data System: Costs of CKD and ESRD. ed. Bethesda, Md., National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007 pp 223-238)—a number that reflects only standard procedural costs and does not include treatment of other complications, emergency procedures, or ancillary procedures such as the placement of vascular grafts for dialysis access. Combined medicare costs for CKD and ESRD in 2005 totaled $62B—representing 19% of all medicare spending for that year (United States Renal Data System: Costs of CKD and ESRD. ed. Bethesda, Md., National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007 pp 223-238). Kidney transplantation is an effective option for stage 4-5 patients as a pre-emptive measure to avoid dialysis or when dialysis is no longer sufficient to manage the disease state, but the number of stage 5 CKD patients in the US (>400,000) who could benefit from whole kidney transplant far exceeds the number of suitable donor kidneys available in any given year (16,000) (Powe, N R et al., Am J Kidney Dis, 53: S37-45, 2009). Thus, new treatment paradigms are needed to delay or reduce dependency on dialysis and to fill the void left by the shortage of donor kidneys.

[0004] Progressive renal disease results from a combination of the initial disease injury (e.g, hypertension), followed by a maladaptive renal response to that injury. Such a response includes the production of pro-inflammatory and pro-fibrotic cytokines and growth factors. Therefore, one strategy to slow CKD progression is to ameliorate the inflammatory and fibrotic response as well as mitigate or reverse renal degeneration through the repair and/or regeneration of renal tissue.

[0005] Chronic renal failure is prevalent in humans as well as some domesticated animals. Patients with renal failure experience not only the loss of kidney function (uremia), but also develop anemia due to the inability of the bone marrow to produce a sufficient number of red blood cells (RBCs) via erythropoiesis. Erythroid homeostasis is dependent on both the production of erythropoietin (EPO) by specialized interstitial fibroblasts that reside in the kidney and the ability of targeted erythroid progenitors in the bone marrow to respond to EPO and manufacture more RBCs. The anemia of renal failure is due to both reduced production of EPO in the kidney and the negative effects of uremic factors on the actions of EPO in the bone marrow.

[0006] To date, clinical approaches to the treatment of chronic renal failure involve dialysis and kidney transplantation for restoration of renal filtration and urine production, and the systemic delivery of recombinant EPO or EPO analogs to restore erythroid mass. Dialysis offers survival benefit to patients in mid-to-late stage renal failure, but causes significant quality-of-life issues. Kidney transplant is a highly desired (and often the only) option for patients in the later stages of renal failure, but the supply of high-quality donor kidneys does not meet the demand for the renal failure population. Bolus dosing with recombinant EPO to treat anemia has now been associated with serious downstream health risks, leading to black box warnings from the FDA for the drug, and necessitating further investigation into alternative treatments to restore erythroid homeostasis in this population. Preclinical investigations have examined in vivo efficacy and safety of EPO-producing cells that have been generated via gene therapy approaches. These studies have shown that it is possible to transiently stimulate erythropoiesis and RBC number by in vivo delivery of epo-producing cells. However, to date, none of these approaches have offered regulated erythroid homeostasis or long-term in vivo functionality. Consequently, HCT and RBC number are often increased beyond normal values, leading to polycythemia vera and other complications. Delivery of EPO-producing cells that are therapeutically-relevant and provide advantages over delivery of recombinant EPO must not only increase HCT, but should restore erythroid homeostasis, with both positive